REMARKS

Upon entry of the above amendment, Claims 1-2, 17-18 and 28-29 will be pending in this application. Claims 1-2, 17-18 and 28-29 have been amended. No new matter has been added. Claims 3-16, 19-27 and 30-47 have been canceled without prejudice or disclaimer.

Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Presently pending independent claim 1 has been amended to recite "a pharmaceutical composition comprising, in admixture, a first active ingredient which is selected from the group consisting of 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] and a pharmaceutically acceptable salt, N-oxide or salt of an N-oxide thereof, and a second active ingredient which is selected from the group consisting of (plus/minus)-[2-[4-(p-chloro-alpha-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid [INN: CETIRIZINE] and a pharmaceutically acceptable salt thereof, wherein the first active ingredient and the second active ingredient are the only active ingredients present in the composition."

Similar amendments have been made to independent claims 17 and 28.

Support for claims 1, 17 and 28 as amended can be found throughout the specification and the claims as originally filed. In particular, basis for reciting the specific active ingredients presently claimed may be found original claims 7, 19 and 30.

Further, the limitation "wherein the first active ingredient and the second active ingredient are the only active ingredients present in the composition" has clear basis in the specification at page 55, 6th paragraph, wherein it states:

> "The invention encompasses on the one hand co-administering **both drugs** in one delivery form such as a fixed oral combination (putting **both active ingredients** in one tablet), as an inhaler (putting **both active ingredients** in the same inhaler) or as a free oral combination (putting **both active ingredients** in two separate tablets). On the other hand it encompasses also the administration of the drugs in **two different delivery forms** such as putting the **PDE4 inhibitor** into **tablets** and package them with **an inhaler** that contains **the histamine receptor antagonist**, or vice versa." (emphasis added)

Thus, the specification provides clear basis for amending the claims to recite only two active ingredients based on 1) the focus on the term "both", therefore meaning "two" and 2) the express recitation of "two different delivery forms", wherein "the PDE4 inhibitor" is in one delivery form and "the histamine receptor antagonist" is in the other.

Accordingly, the claims have been amended to include only the active compounds recited. Applicants respectfully point out, however, that the pharmaceutical compositions of claim 1-2, the pharmaceutical products of claims 17-18 and the kits of claims 28-29 can contain additional elements such as excipients and/or vehicles in view of the transitional term "comprising" in these claims.

In view of the claim amendments as well as the remarks set forth below, further and favorable consideration is respectfully requested and an early allowance of this application is earnestly solicited.

I. At page 3 of the Official Action, claims 2-9, 11, 18-21, 23, 29, 30, 41 and 42 have been objected to.

The Examiner states that "Applicant is encouraged to replace the term 'A' with the term 'The' at the beginning of the claims. The aforementioned claims are dependent claims.

RESPONSE

Regarding claims 3-9, 11, 19-21, 23, 30, 41 and 42, applicants respectfully point out that these claims have been cancelled, rendering the basis for this objection moot as to these claims.

Regarding claims 2, 18 and 29, applicants respectfully note that these claims have been amended to recite "The" instead of "A" at the beginning of each claim.

Withdrawal of this objection is respectfully requested.

II. At page 4 of the Official Action, claims 2, 11, 18, 23, 29, 32, 41, 42 and 45 are rejected under 35 U.S.C §112, first paragraph.

The Examiner states that claims 2, 11, 18, 23, 29, 32, 41, 42 and 45 are rejected under 35 U.S.C. §112, first paragraph "because the specification, while enabling for the first and second active ingredient, e.g. roflumilast and cetirizine, respectively, their pharmaceutically acceptable salts, N-oxide and salt of an N-oxide, does not reasonably provide enablement for their hydrate, solvate, hydrate of a salt, solvate of a salt, hydrate of an N-oxide, or solvate of an N-oxide."

RESPONSE

Regarding claims 11, 23, 32, 41, 42 and 45, applicants respectfully point out that these claims have been cancelled, rendering the basis for this rejection moot as to these claims.

Regarding claims 2, 18 and 29, applicants respectfully traverse. However, solely to advance prosecution, applicants note that these claims have been amended to recite the language that the Examiner has conceded is enabled.

Reconsideration and withdrawal of this rejection is respectfully requested.

III. At pages 8-10 of the Official Action, claims 1-6, 17, 18, 28, 29, 41, 42 and 45 are rejected under 35 U.S.C §112, first and second paragraphs.

The Examiner states that claims 1-6, 17, 18, 28, 29, 41, 42 and 45 are rejected under 35 U.S.C. §112, first and second paragraphs for reciting the phrase "pharmaceutically acceptable derivatives". The rejection under 35 U.S.C. §112, first paragraph is for failing to comply with the written description requirement. The rejection under 35 U.S.C. §112, second paragraph is for indefiniteness.

RESPONSE

Regarding claims 3-6, 41, 42 and 45, applicants respectfully point out that these claims have been cancelled, rendering the basis for this rejection moot as to these claims.

Regarding claims 1-2, 17-18 and 28-29, applicants respectfully traverse. However, solely to advance prosecution, applicants note that these claims have been amended to delete the phrase "pharmaceutically acceptable derivatives".

Reconsideration and withdrawal of this rejection is respectfully requested.

IV. At page 10 of the Official Action, claims 1, 5, 7-9, 11, 17, 19-21, 23, 41, 42 and 45 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gamache et al. (U.S. Patent No. 6,174,878).

Claims 1, 5, 7-9, 11, 17, 19-21, 23, 41, 42 and 45 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gamache et al. (U.S. Patent No. 6,174,878). The Examiner alleges that Gamache et al. disclose compositions adapted for intranasal administration for the treatment of otic tissues, wherein the composition may be in the form of nasal drops or an aerosol composition.

RESPONSE

Regarding claims 5, 7-9, 11, 19-21, 23, 41, 42 and 45, applicants respectfully point out that these claims have been cancelled, rendering the basis for this rejection moot as to these claims.

Regarding presently pending claims 1 and 17, applicants respectfully traverse.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U. S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple

patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a proper case of *prima facie* obviousness has not been established because the cited reference does not teach or suggest all the limitations of the claims as required by *In re Wilson*. Further, a skilled artisan would never be motivated to modify the teachings of the cited reference to arrive at the presently pending claims with any reasonable expectation of success as required by *Amgen Inc. v. Chugai Pharm Co.*

Independent claim 1 is directed to "a pharmaceutical composition comprising, in admixture, a first active ingredient which is selected from the group consisting of 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN:

ROFLUMILAST] and a pharmaceutically acceptable salt, N-oxide or salt of an N-oxide thereof, and a second active ingredient which is selected from the group consisting of (plus/minus)-[2-[4-(p-chloro-alpha-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid [INN: CETIRIZINE] and a pharmaceutically acceptable salt thereof, wherein the first active ingredient and the second active ingredient are the only active ingredients present in the composition.

Independent claim 17 is directed to "a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is selected from the group consisting of 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] and a pharmaceutically acceptable salt, N-oxide or salt of an N-oxide thereof, and a preparation of a second active ingredient which is selected from the group consisting of (plus/minus)-[2-[4-(p-chloro-alpha-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid [INN: CETIRIZINE] and a pharmaceutically acceptable salt thereof, for simultaneous, sequential or separate use in therapy, wherein the first active ingredient and the second active ingredient are the only active ingredients present in the pharmaceutical product.

The Examiner will note that the pharmaceutical composition of claim 1 and the pharmaceutical product of Claim 17 have each been amended so that no additional active ingredients other than the named active ingredients may be present in the presently claimed subject matter. Applicants respectfully point out, however, that the pharmaceutical composition of claim 1 and the pharmaceutical product of claims 17 may contain additional elements such as excipients and/or vehicles in view of the transitional term "comprising" in these claims.

In contrast to the presently claimed subject matter, Gamache et al. describe the use of a kappa opioid agonist compound which may be combined with another active ingredient such as an anti-allergy agent such as cetirizine or an anti-inflammatory agent such as roflumilast.

Accordingly, Gamache et al. require the presence of a kappa opioid agonist. The presently pending claims specifically exclude any other active ingredients other than those recited in view of the claim limitation "wherein the first active ingredient and the second active ingredient are the only active ingredients present in the composition". Accordingly, Gamache et al. does not "teach or suggest all the limitations of the claims" as required by *In re Wilson.*

Further, a skilled artisan would never be motivated to modify the teachings of the Gamache et al. reference to arrive at the presently pending claims with any reasonable expectation of success as required by *Amgen Inc. v. Chugai Pharm Co.* Gamache et al. require the presence of a kappa opioid agonist. Cetirizine and Roflumilast are only discussed by Gamache et al. as two of many alternative "additional pharmaceutically active agents" at col. 5, line 35 that can be combined with the kappa opioid agonist. Thus, the ordinary skilled artisan would not be motivated by the teachings of the cited references to eliminate the presence of the kappa opioid agonist and only include "additional pharmaceutically active agents" such as the presently claimed Citirizine and Roflumilast compounds. As such, the Gamache et al. reference does not render the presently pending claims obvious.

Accordingly, Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because the cited reference does not teach or

suggest all the limitations of the claims as required by *In re Wilson*. Further, a skilled artisan would never be motivated to modify the teachings of the cited reference to arrive at the presently pending claims with any reasonable expectation of success as required by *Amgen Inc. v. Chugai Pharm Co.*

As such, the Examiner has failed to demonstrate a *prima facie* case of obviousness against pending claims 1 and 17. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

V. At page 12 of the Official Action, claims 2-4, 6, 18, 28-30 and 32 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gamache et al. (U.S. Patent No. 6,174,878) in view of Bratzler et al. (U.S. Patent Application Publication No. 2004/0067902).

Claims 2-4, 6, 18, 28-30 and 32 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gamache et al. (U.S. Patent No. 6,174,878) in view of Bratzler et al. (U.S. Patent Application Publication No. 2004/0067902).

RESPONSE

Regarding claims 3-4, 6, 30 and 32, applicants respectfully point out that these claims have been cancelled, rendering the basis for this rejection moot as to these claims.

Regarding presently pending claims 2, 18, 28 and 29, applicants respectfully traverse.

A brief outline of relevant authority for establishing a *prima facie* case of obviousness is set forth above in Section IV and is incorporated herein by reference.

A discussion of the Gamache et al. reference is also set forth above in Section IV. and is incorporated herein by reference.

The Bratzler et al. reference does not remedy the deficient teachings of the Gamache et al. reference. In fact, Bratzler et al. also requires an active ingredient that is not present in the presently claimed subject matter. In particular, Bratzler et al. require the presence of an immunostimulatory nucleic acid as part of the composition. Active ingredients such as those presently claimed are only listed as possible "asthma / allergy medicaments" to be combined with the nucleic acid. See [0035] and [0036].

Accordingly, Bratzler et al. require the presence of an immunostimulatory nucleic acid. The presently pending claims specifically exclude any other active ingredients other than those recited in view of the claim limitation "wherein the first active ingredient and the second active ingredient are the only active ingredients present in the composition". Accordingly, Bratzler et al. does not "teach or suggest all the limitations of the claims" as required by *In re Wilson.*

Further, a skilled artisan would never be motivated to modify the teachings of the Bratzler et al. reference to arrive at the presently pending claims with any reasonable expectation of success as required by *Amgen Inc. v. Chugai Pharm Co.* Bratzler et al. require the presence of an immunostimulatory nucleic acid. PDE4 inhibitors generally are only discussed by Bratzler et al. as possible "asthma / allergy medicaments" to be combined with the nucleic acid. See [0035]. Bratzler et al. do not even mention the specific PDE4 inhibitor Roflumilast. Cetirizine is only discussed by Bratzler et al. as a possible "asthma / allergy medicament" to be combined with the nucleic acid. See [0036].

Thus, the ordinary skilled artisan would not be motivated by the teachings of the cited references to eliminate the presence of the nucleic acid and only include possible "asthma / allergy medicament" compounds such as the presently claimed Citirizine and Roflumilast compounds. As such, the Bratzler et al. reference does not render the presently pending claims obvious.

Accordingly, Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because the cited references do not teach or suggest all the limitations of the claims as required by *In re Wilson*. Further, a skilled artisan would never be motivated to modify the teachings of the cited references to arrive at the presently pending claims with any reasonable expectation of success as required by *Amgen Inc. v. Chugai Pharm Co.*

As such, the Examiner has failed to demonstrate a *prima facie* case of obviousness against pending claims 2, 18, 28 and 29. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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